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## Structure analysis of streptococcal protein G Fc binding domain.

Cai SY, Wang YY, Yao ZJ.

Laboratory of Protein Chemistry, Institute of Basic Medical Sciences, Beijing, PRC.

The gene fragment (191 bp) encoding protein G IgG Fc binding domain was isolated by PCR from group G streptococcus (CMCC32138), and a clone containing this gene fragment was found to give fine reactivity to human IgG when expressed in *Escherichia coli*. The complete nucleotide sequence of the gene fragment was determined. One base pair differs from previously reported protein G nucleotide sequences, and results in an amino acid change (Ala-Thr), but this variation makes no difference in binding to the IgG Fc part by ELISA. The secondary structure of the protein G IgG Fc binding domain has been estimated by circular dichroism and assigned by computer algorithm. It shows a typical alpha-helix region in this domain. By breaking this alpha-helix region with recombinant DNA techniques, a 44 peptide, which contained the N-terminal 27 amino acid residues of this domain, was expressed in *E. coli* and showed no reactivity to IgG. The hydropathicity of this domain was also analyzed and compared with that of protein A relevant domain. Some similarity was found. These results suggest that the binding mechanism of protein G to the IgG Fc part depends on hydrophobic action which comes from the alpha-helix in protein G molecule, just as protein A binding to IgG Fc part.

PMID: 8503988 [PubMed - indexed for MEDLINE]

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## Di-, tri- and tetrameric single chain Fv antibody fragments against human CD19: effect of valency on cell binding.

Le Gall F, Kipriyanov SM, Moldenhauer G, Little M.

Recombinant Antibody Research Group, German Cancer Research Center (DKFZ), Heidelberg, Germany.

Single chain variable fragments (scFv) of the murine monoclonal antibody HD37 specific to human B-cell antigen CD19 were constructed by joining the VH and VL domains with linkers of 18, 10, 1 and 0 residues. ScFv-18 formed monomers, dimers and small amounts of tetramers; scFv-10 formed dimers and small amounts of tetramers; scFv-1 formed exclusively tetramers; scFv-0 formed exclusively trimers. The affinities of the scFv-1 (diabody) and scFv-1 (tetrabody) were approximately 1.5- and 2.5-fold higher, respectively, than that of the scFv-0 (triabody). The tetrabody displayed a significantly prolonged association with cell-bound antigen (t<sub>1/2</sub> cell surface retention at 37 degree C of 26.6 min) compared to both the diabody (13.3 min) and triabody (6.7 min). This increase in avidity of the tetrabody combined with its larger size could prove to be particularly advantageous for imaging and the immunotherapy of B-cell malignancies.

PMID: 10403395 [PubMed - indexed for MEDLINE]

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1: J Mol Biol 1995 Feb 10;246(1):28-34

[Related Articles, Li](#)**ELSEVIER SCIENCE  
FULL-TEXT ARTICLE**

## Tetravalent miniantibodies with high avidity assembling in Escherichia coli.

Pack P, Muller K, Zahn R, Pluckthun A.

Biochemisches Institut Universitat Zurich, Switzerland.

We have designed tetravalent miniantibodies assembling in the periplasm of Escherichia coli. They are based on single-chain F fragments, connected via a flexible hinge to an amphipathic helix which tetramerizes the molecule. The amphipathic helix is derived from the coiled coil helix of the transcription factor GCN4, in which all hydrophobic a positions of every heptad repeat have been exchanged to leucine and all d positions to isoleucine. Gel filtration shows tetramer assembly of the miniantibody even at low concentrations. As expected, the functional affinity (avidity) of the tetravalent miniantibody is higher in ELISA and BIAcore measurements than that of the bivalent construct and the gain is dependent on surface epitope density.

PMID: 7853401 [PubMed - indexed for MEDLINE]

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Comment in:

- [Nat Biotechnol. 1997 Feb;15\(2\):125-6.](#)

## Design and production of novel tetravalent bispecific antibodies.

Coloma MJ, Morrison SL.

Department of Microbiology and Molecular Genetics, University of California at Los Angeles 90095, USA.

We have produced novel bispecific antibodies by fusing the DNA encoding a single chain antibody (ScFv) after the C terminus (CH3-ScFv) or after the hinge (Hinge-ScFv) with an antibody of a different specificity. The fusion protein is expressed by gene transfection in the context of a murine variable region. Transfectomas secrete a homogeneous population of the recombinant antibody with two different specificities, one at the N terminus (anti-dextran) and one at the C terminus (anti-dansyl). The CH3-ScFv antibody, which maintains the constant region of human IgG3, has some of the associated effector functions such as long half-life and Fc receptor binding. The Hinge-ScFv antibody which lacks the CH2 and CH3 domains has no known effector functions.

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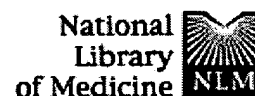
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## Multivalent antibody fragments with high functional affinity for a tumor-associated carbohydrate antigen.

Rheinnecker M, Hardt C, Ilag LL, Kufer P, Gruber R, Hoess A, Lupas A, Rottenberger C, Pluckthun A, Pack P.

MorphoSys GmbH, Munich, Germany.

We report in this work a human-derived self-assembling polypeptide based on the tetramerization domain of the human transcription factor p53, which can be fused to single-chain Fv Ab (scFv) fragments via a long and flexible hinge sequence of human origin, allowing exploitation of the functional affinity increase of binding to a ligand or cell surface with multimeric binding sites. We have demonstrated the use of this polypeptide by applying it to the construction of a tetrameric scFv against the tumor-associated carbohydrate Ag Lewis Y (Fuc alpha 1-->2Gal beta 1-->4[Fuc alpha 1-->3] GlcNAc beta 1-->3R). For comparison purposes, the corresponding scFv and dimeric mini-antibody, comprising the scFv fused via a flexible murine hinge and an artificial dimerization domain, were also created. The recombinant mini-antibody proteins were expressed in functional form in *Escherichia coli* and showed the expected m.w. of a dimer and tetramer, respectively. Analysis of Lewis Y-binding behavior by surface plasmon resonance revealed specific but very weak binding of the scFv fragment. In contrast, both dimeric and tetrameric scFv fusion proteins exhibited an enormous gain in functional affinity that was greatest in the case of the tetrameric mini-antibody.

PMID: 8816407 [PubMed - indexed for MEDLINE]

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14401711 22403547 PMID: 12515168

[Construction and screening of type 1 human immunodeficiency virus specific phage antibodies combinatorial library]

He Y; Wang X; Liu S

Research Center of Virology, Beijing Ditan Hospital, Beijing 100011.

Zhonghua shi yan he lin chuang bing du xue za zhi = Zhonghua shiyan he linchuang bingduxue zazhi = Chinese journal of experimental and clinical virology (China) Mar 1998, 12 (1) p33-7, ISSN 1003-9279

Journal Code: 9602873

Document type: Journal Article ; English Abstract

Languages: CHINESE

Main Citation Owner: NLM

Record type: Completed

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Human monoclonal antibodies to type 1 immunodeficiency virus (HIV-1) gp120 were generated from phage antibody combinatorial library. METHODS: The human immunoglobulin heavy chain Fd and light chain k genes were amplified by half-nested PCR from PBMC of patient infected with HIV. Phage antibody combinatorial library was constructed with the Fd and k chain genes using Pcomb3 as vector. The affinity selection and ELISA were adopted for generating specific phage antibodies. Partial DNA of a positive clone was sequenced and its soluble Fab was expressed in E coli. HIV-1 specific phage antibodies combinatorial library were constructed using the Fd and k genes and Pcomb3 vector. The library capacity was about  $1.95 \times 10^7$ . The specific phage antibodies were highly enriched after three rounds of biopanning selection against HIV-1 gp120 and 32% positive clones were detected by ELISA screening. DNA fragment coding for CH1 and CL derived from a positive clone was sequenced and its product was successfully expressed as soluble Fab which was specific for HIV-1 gp120. The HIV-1 specific phage antibody combinatorial library, and human monoclonal antibodies to HIV-1 gp120 have been used as tools for screening of neutralizing antibody to HIV-1, and the methods seem to be very crucial and applicable.

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13271511 21060022 PMID: 10542098

**Structure of the TRAIL- DR5 complex reveals mechanisms conferring specificity in apoptotic initiation.**

Mongkolsapaya J; Grimes J M; Chen N; Xu X N; Stuart D I; Jones E Y; Screaton G R

MRC Human Immunology Unit, Institute of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DS, UK.

Nature structural biology (United States) Nov 1999, 6 (11) p1048-53, ISSN 1072-8368 Journal Code: 9421566

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Subfile: INDEX MEDICUS

TRAIL, an **apoptosis** inducing ligand, has at least four cell surface receptors including the death receptor **DR5**. Here we report the crystal structure at 2.2 Å resolution of a complex between TRAIL and the extracellular region of **DR5**. TRAIL forms a central homotrimer around which three **DR5** molecules bind. Radical differences in the surface charge of the ligand, together with variation in the alignment of the two receptor domains confer specificity between members of these ligand and receptor families. The existence of a switch mechanism allowing variation in receptor domain alignment may mean that it is possible to engineer receptors with multiple specificities by exploiting contact positions unique to individual receptor-ligand pairs.

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10533762 20065110 PMID: 10597242

**Induction of the TRAIL receptor KILLER/ DR5 in p53-dependent apoptosis but not growth arrest.**

Wu G S; Burns T F; McDonald E R; Meng R D; Kao G; Muschel R; Yen T; el-Deiry W S

Department of Medicine, Howard Hughes Medical Institute, University of Pennsylvania School of Medicine Philadelphia 19104, USA.

Oncogene (ENGLAND) Nov 11 1999, 18 (47) p6411-8, ISSN 0950-9232 Journal Code: 8711562

Contract/Grant No.: CA75138-01; CA; NCI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

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The TRAIL death receptor KILLER/ **DR5** is induced by DNA damaging agents in wild-type p53-expressing cells. Here we show that, unlike the p53-target CDK-inhibitor p21WAF1/CIP1, the TRAIL death receptor KILLER/ **DR5** is only induced in cells undergoing p53-dependent **apoptosis** and not cell cycle arrest. Thus GM glioblastoma cells carrying an inducible MMTV-driven p53 gene undergo cell cycle arrest and upregulate p21 but not KILLER/ **DR5** expression upon dexamethasone exposure. WI38 normal lung fibroblasts undergoing cell cycle arrest in response to ionizing irradiation also induce p21 but not KILLER/ **DR5** gene expression. KILLER/ **DR5** upregulation is also deficient in irradiated lymphoblastoid cells derived from patients with Ataxia Teleangiectasia suggesting a role for the ATM-p53 pathway in regulating KILLER/ **DR5** expression after DNA damage. Inhibition of transcription by Actinomycin D blocks both KILLER/ **DR5** and p21 induction in cells undergoing p53-dependent **apoptosis**. Our results suggest that the p53-dependent transcriptional induction of KILLER/ **DR5** death receptor is restricted to cells undergoing **apoptosis** and not cells undergoing

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10503631 20047509 PMID: 10582684



**Alterations of the DR5 /TRAIL receptor 2 gene in non-small cell lung cancers.**

Lee S H; Shin M S; Kim H S; Lee H K; Park W S; Kim S Y; Lee J H; Han S Y; Park J Y; Oh R R; Jang J J; Han J Y; Lee J Y; Yoo N J

Department of Pathology, College of Medicine, The Catholic University of Korea, Seoul.

Cancer research (UNITED STATES) Nov 15 1999, 59 (22) p5683-6, ISSN 0008-5472 Journal Code: 2984705R

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

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Chromosome 8p21-22 is a frequent site of allelic deletions in many types of human tumors, including non-small cell lung cancer (NSCLC). Tumor necrosis factor-related **apoptosis** -inducing ligand-receptor 2 (TRAIL-R2) is a cell-surface receptor involved in cell death signaling. The TRAIL-R2 gene recently has been mapped to chromosome 8p21-22. To explore the possibility that the TRAIL-R2 gene might be the relevant gene to the frequent deletion of 8p21-22 in NSCLC, we have analyzed the entire coding region and all splice sites of TRAIL-R2 for the detection of the somatic mutations in a series of 104 NSCLCs. Overall, 11 tumors (10.6%) were found to have TRAIL-R2 gene mutations in the death domain known to be involved in the transduction of an **apoptotic** signal. Our data indicate that somatic mutation of TRAIL-R2 may play a role in the pathogenesis of some NSCLCs and that the TRAIL-R2 gene is one of the genes relevant to the frequent loss of chromosome 8p21-22 in NSCLC.

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10491759 20016594 PMID: 10548878

**Control of apoptosis signaling by Apo2 ligand.**

Marsters S A; Pitti R A; Sheridan J P; Ashkenazi A

Department of Molecular Oncology, Genentech, Inc, South San Francisco, California 94080, USA.

Recent progress in hormone research (UNITED STATES) 1999, 54 p225-34, ISSN 0079-9963 Journal Code: 0404471

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

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Apo2 ligand (Apo2L, also called TRAIL) is a member of the tumor necrosis factor (TNF) cytokine family. The closest homolog of Apo2L is CD95 (Fas/Apo1) ligand, to which it has 24% amino acid sequence identity. Similar to CD95L, Apo2L activates rapid **apoptosis** in many types of cancer cells; however, whereas CD95L mRNA expression is restricted mainly to activated T cells, natural killer cells, and immune-privileged sites, Apo2L mRNA occurs in a wide variety of tissues. Most normal cells appear to be resistant to Apo2L's cytotoxic action, suggesting the existence of mechanisms that can protect against **apoptosis** induction by Apo2L. The first receptor described for Apo2L, called death receptor 4 (DR4), contains a cytoplasmic "death domain"; DR4 transmits the **apoptosis** signal carried by Apo2L. We have identified three additional receptors that bind to Apo2L. One receptor, called **DR5**, contains a cytoplasmic death domain and signals **apoptosis** much like DR4. The DR4 and **DR5** mRNAs are expressed in many normal tissues and tumor cell lines. The second receptor, designated decoy receptor 1 (Dcr1), is a phospholipid-anchored cell-surface protein that lacks a cytoplasmic tail. The third receptor, called Dcr2, is structurally similar to DR4 and **DR5** but has a truncated cytoplasmic death domain and does not transmit a death signal. The mRNAs for Dcr1 and Dcr2 are expressed in multiple normal tissues but in few tumor cell lines. Transfection experiments indicate that Dcr1 and Dcr2 act as decoys that prevent Apo2L from inducing **apoptosis** through DR4 and **DR5**. These decoy receptors thus represent a novel mechanism for regulating sensitivity to a pro- **apoptotic** cytokine directly at the cell's surface. The preferential expression of these inhibitory receptors in normal tissues suggests that Apo2L may be useful as an anticancer agent that induces **apoptosis** in cancer cells

while sparing normal cells. (26 Refs.)

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10485355 20017054 PMID: 10549288

**Triggering cell death: the crystal structure of Apo2L/TRAIL in a complex with death receptor 5.**

Hymowitz S G; Christinger H W; Fuh G; Ultsch M; O'Connell M; Kelley R F; Ashkenazi A; de Vos A M

Department of Protein Engineering, Genentech, Inc., South San Francisco, California 94080, USA.

Molecular cell (UNITED STATES) Oct 1999, 4 (4) p563-71, ISSN 1097-2765 Journal Code: 9802571

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

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Formation of a complex between Apo2L (also called TRAIL) and its signaling receptors, DR4 and DR5, triggers **apoptosis** by inducing the oligomerization of intracellular death domains. We report the crystal structure of the complex between Apo2L and the ectodomain of DR5. The structure shows three elongated receptors snuggled into long crevices between pairs of monomers of the homotrimeric ligand. The interface is divided into two distinct patches, one near the bottom of the complex close to the receptor cell surface and one near the top. Both patches contain residues that are critical for high-affinity binding. A comparison to the structure of the lymphotoxin-receptor complex suggests general principles of binding and specificity for ligand recognition in the TNF receptor superfamily.

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10482573 20016204 PMID: 10550011

**Apoptosis and drug response.**

Houghton J A

Department of Molecular Pharmacology, St. Jude Children's Research Hospital, Memphis, Tennessee 38105, USA.

Current opinion in oncology (UNITED STATES) Nov 1999, 11 (6) p475-81

, ISSN 1040-8746 Journal Code: 9007265

Document type: Journal Article; Review; Review, Tutorial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

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Recent investigation further defines the role of p53 and of signaling events upstream and downstream of p53 in **apoptosis** following drug-induced DNA damage. The transcription factors NF-kappaB and AP-1 can be activated, and then directly transactivate FasL in response to chemotherapeutic agents. Death receptors for FasL (Fas) and for TRAIL (DR4, DR5) are emerging as important regulators of drug-induced **apoptosis** in human cancers, mediated by caspase activation. **Apoptosis** has been accepted as the predominant mechanism of drug-induced cell death in preclinical experimental models and in clinically sensitive tumors. However, drug-induced cell death can include acute or delayed **apoptosis**, necrosis, or a delayed mitotic death, and require further delineation for their relative contribution to tumor responses in vivo. (70 Refs.)